Claim 65 is rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled. The Examiner contends that the non-pathogenic HIV-isolates having the designations V94101706, V941031169, and V95031022 are required to practice the claimed methodology. The Examiner indicates that the rejection can be overcome by making a deposit of the strains recited in claim 65 in accordance with the provisions of 37 C.F.R. §1.802.

It is respectfully submitted that the rejection of claim 65 is rendered moot in view of the cancellation of claim 65 without prejudice. It is further submitted that HIV-isolates having the designations V94101706, V941031169, and V95031022 are presently recited in claims 123, 126, 133 and 136. Applicants respectfully submit that these viruses were deposited at the PHLS Centre for Applied Microbiology and Research, European Collection of Animal Cell Cultures (ECACC), Division of Biologies, Porton Down, Salisbury, Wiltshire SP4 OJG. Copies of the receipts of these deposits are provided herewith as (**Exhibit A**). Applicants submit that all restrictions on availability of these viruses to the public will be irrevocably removed upon the granting of the patent based upon the captioned application and the viruses will remain permanently available for a term of at least 5 years after the most recent request for the furnishing of a sample, and in any case, for a period of at least 30 years after the date of deposit or for the enforceable life of the U.S. patent whichever is longer. In the event that the viruses become non-viable or are inadvertently destroyed, such will be replaced with viable viruses of the same taxonomic description.

Claims 49-67 and 85 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support.

In the first instance, Applicants respectfully direct the Examiner's attention to the amendment to the claims. Specifically, claims 49-50, 66-67 and 85 have been amended; claims

51-65 have been canceled without prejudice; and claims 120-136 have been added. As presently recited, claims 49-50, 66-67 and 120-126 are drawn to methods of vaccinating an individual against AIDS or AIDS-related diseases by administering a non-pathogenic HIV-1 isolate for the patent. Claims 85 and added claims 127-136 are drawn to therapeutic compositions useful for inhibiting productive infection by a pathogenic strain of HIV, which compositions comprise a non-pathogenic HIV-1 isolate. The non-pathogenic HIV-1 isolate in the present claims are defined by the underlying alterations of the *nef* gene and the LTR region. Support for the amendment to claims 49-50, 66-67 and 85 and for added claims 120-136 is found in the specification. Specific support for the recitation of "deletion in the region corresponding to nucleotides 9281-9438 of the *nef* gene and U3 long terminal repeat", as found in claims 49 and 85 as amended, is provided by the instant disclosure as follows.

First, at page 45, line 11 of the specification, the deletion of nucleotides 9281-9371 is specifically disclosed. In addition, at page 28, lines 10-11, the present specification discloses that a mutation in the LTR region of a non-pathogenic HIV-1 isolate occurs 5' of the Sp1 sites. Applicants respectfully submit that the first Sp1 site in the LTR occurs immediately after nucleotide 9438. Figure 5 also indicates mutations beyond nucleotide 9419 in the NFkB region of the LTR prior to the SpI sites.

Moreover, a deletion of nucleotides 9281-9438 is apparent to one skilled in the art by comparing SEQ ID NO: 614 or SEQ ID NO: 615 with the wild type HIV-1 sequence. Specifically, Applicants submit that nucleotide 9281 begins after the fourth T on line 22 of page 40 of the subject specification where SEQ ID NO:614 (D36) is disclosed. The sequence prior to 9281 is ATTGTT. The next nucleotide would be 9281 and is the beginning of the deletion. The deletion extends to nucleotide 9439 which can be seen after the fifth G on line 23. The

nucleotide sequence in SEQ ID NO: 614 between position 9281 and position 9439 is the result of "fill in" and duplication, which is amply described in the specification. Thus, the existence of the deletion from 9281-9439 is clear to a skilled artisan by comparing SEQ ID NO: 614 with the nucleotide sequence of the corresponding region in wild type HIV-1 strain NL4-3 (SEQ ID NO: 1). Similarly, SEQ ID NO: 615 (C18) on (pages 40-41) of the subject specification shows the same deletion, i.e., nucleotides 9281-9439. The beginning of the nucleotide deletion, i.e., nucleotide 9281 occurs after the fourth T on line 8 of page 41. The deletion ends after the eighth C on line 9 of page 41. The existence of deletion 9281-9439 is thus clear to a skilled artisan by comparing SEQ ID NO: 615 with the wild type sequence of NL4-3 (SEQ ID NO: 1).

In support of the above sequence data, Applicants provide a copy of the declaration of Dr. Nicolas Deacon as (**Exhibit B**), which declaration was submitted in the prosecution of the parent case Serial No. 08/388,353 (now U.S. Patent No. 6,010,895). Accordingly, Applicants respectfully submit that the recitation of "deletion in the region corresponding to nucleotides 9281-9438 of the *nef* gene and U3 long terminal repeat" is adequately supported by the specification.

Turning to the Examiner's contentions respecting the enablement rejection, the Examiner identifies various literature references including Kirchof et al., Huang et al., Michael et al. and Terwillinger et al. (each bearing a post-filing date of publication) which allegedly suggest that alterations in the *nef* gene may not be a common basis for the absence of the progression of HIV infection or AIDS. The Examiner also contends that the specification does not disclose which components, parts, fragments or derivatives thereof, contain the molecular determinants governing pathogenicity. In addition, the Examiner contends that the specification does not set forth the criteria for ascertaining the pathogenic properties of any given variant. Moreover, the

Examiner alleges that the specification fails to demonstrate that the instant non-pathogenic HIV variants would mount an efficacious humoral or cellular immune response resulting in the prevention or treatment of HIV-infection and the clinical sequelae leading to AIDS.

Applicants respectfully submit that the present invention is predicated in part upon the discovery of a cohort of individuals which are related to one another only as recipients of blood from a single donor who was HIV-1 positive. In this respect, the present invention is set apart from the state of the art in that alterations in the *nef* gene or U3 region of the LTR, as presently claimed, define a nexus for the non-pathogenicity among these patients. None of the cohort members have developed any symptoms of AIDS, now after 14 years, while the median time for developing AIDS is four to six years. The cohort members including the donor are unique in that, despite having antibodies to HIV glycoproteins (HIV positive), these patients have no immunological evidence of immune system damage such as altered CD4+ counts, altered β_2- microglobulin concentrations or absence of cytotoxic T cells. Each of the cohorts including the donor however were infected with the AIDS virus, albeit a non-pathogenic strain as defined by the claimed alterations in the *nef* gene or U3 region of the LTR.

Applicants further submit that, contrary to the Examiner's allegation, non-pathogenicity and its determination in the present context, is set forth in the specification at pages 19-21 of the specification, for example. The terms are defined uniquely at a clinical level as well as, more commonly, at the laboratory level. Thus, one skilled in the art can readily determine non-pathogenic strains of HIV-1 in accordance with the present invention.

As to the literature references including Kirchof et al., Huang et al. and Michael et al., the Examiner is of the opinion that these references suggest that alterations in the *nef* gene may not be a common basis for the absence of the progression of HIV infection of AIDS. In the first

instance, Applicants submit that these conclusions and underlying data are highly inconclusive, even speculative. Moreover, that other mechanisms may influence the pathogenicity of HIV-1 is not the point. The fact that the literature identifies other factors effecting pathogenicity is expected considering the complexity of the HIV genome and the interaction between virus and host. However, none of these observations negate the patentability of the present invention, i.e., alterations in a particular region of the *nef* gene or LTR clearly result in the non-pathogenicity of the exemplified strains, and such non-pathogenic strains can be used as vaccines against pathogenic HIV strains.

Terwillinger et al. appear to suggest the varying influence of allelic variations of *nef* on virus replication. The HIV-1 strains recited in the present claims comprise a deletion in the *nef* or LTR regions which effect the observed and intended in vivo result. Allelic variation is not determinative, as with many factors which affect phenotypic properties; mutations of the *nef* or LTR region define the HIV-1 isolates employed in the present methods.

Applicants further direct the Examiner's attention to the Declaration by Dr. Deacon (**Exhibit B**), which declaration supports the nexus between the deletion in the *nef* or LTR region and the non-pathogenicity of the HIV-isolates recited in the present claims. Specifically, as provided in the declaration, isolate C18 has been completely sequenced and evidences no differences from the wild type HIV strain except for the mutation corresponding to amino acids 166-206 of the *nef* gene and extending into the U3 region of the LTR (Paragraph 12). Full length sequences for clones C54, C98 and D36 have also been determined by the present inventors with consistent results (Paragraph 12). Those individuals infected with the subject HIV-1 strains do not exhibit AIDS symptoms over time; indeed the individuals exhibit normal CD4+ levels. Thus, it is respectfully submitted that, while non-pathogenicity can be effected in many ways, the

deletions in the present HIV-1 isolates offer a consistent basis of attenuation which is clinically measurable on live individuals.

As to the alleged failure to show an immune response invoked by the instant non-pathogenic HIV variants, Applicants respectfully submit that the protective effects of the non-pathogenic HIV-1 strains are not necessarily achieved by, or achieved solely by, the induction of a cellular or humoral or immune response in a vaccinated subject. The basis of the vaccination may involve competition for receptors, incompatibility or genomic restrictions.

However, Applicants submit that those skilled in the art can, if desired, determine the extent of the immune responses induced by the non-pathogenic HIV-strains using techniques readily available in the art. As support of such position, Applicants provide herewith a report paper by Dyer et al. (*J. Virol. 73*: 436-443, 1999) (**Exhibit C**) regarding the effectiveness of the Sydney Blood Bank Cohort (SBBC) strain of HIV-1 as an immunogen. Dyer et al. describe the cellular immune responses induced by members of the SBBC. In the study, the donor (D36) and the six recipients were studied for HIV-1 specific cytotoxic T-cell activity by four techniques. Four (D36, C18, C49, C98) of the seven had strong anti-HIV-1 responses, and one (C135) had no detectable response. It is also known (although not reported in this paper) that all SBBC members, except C135, had strong antibody responses including Western blot.

In view of the foregoing remarks, it is respectfully submitted that the enablement rejection under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is therefore respectfully requested.

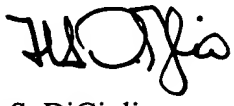
Claim 85 is rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for depending from non-elected claims 1-16.

It is respectfully submitted that claim 85 as presently amended is an independent claim. Added claims 127-136 are also drawn to therapeutic compositions comprising a nonpathogenic isolate of HIV-1. Support for the amendment to claim 85 and for the added claims 127-136 are found in the specification and in original claims 1-16. Support for the recitation of "nucleotides 9281-9438" in claims 85 and 134 is found in the specification, as submitted above. As such, the rejection of claim 85 under 35 U.S.C. §112, second paragraph, is obviated. Withdrawal of the rejection is therefore respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the instant amendment. The attached page is captioned "**Version with Markings to Show Changes Made.**"

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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Exhibits A-C